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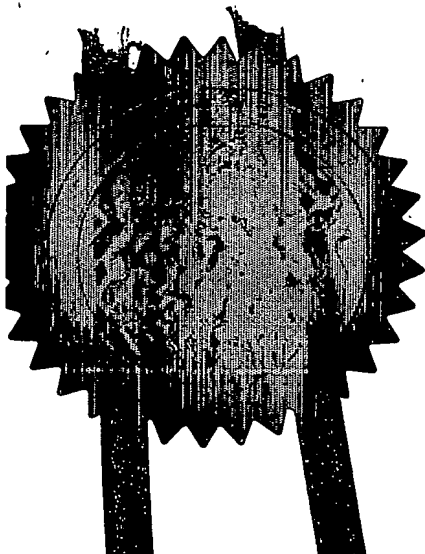
PCT/EP 03/11648

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The
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P01/7700 0.00 0224494.5

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your Reference JAF/PG4978

2. Patent application number 0224494.5
(The Patent office will fill in this part)

3. Full name, address and postcode of the or of each applicant (underline all surnames)
GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

22 OCT 2002

Patents ADP number (if you know it)

473587003

If the applicant is a corporate body, give the country/state of its corporation GB

4 Title of the invention MEDICINAL COMPOUNDS

5 Name of your agent (if you know one) JUDITH PRITCHARD

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)
GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY
980 GREAT WEST ROAD
BRENTFORD, MIDDLESEX
TW8 9GS, GB

Patents ADP number (if you know it)

8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? (Answer yes if:
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

9. Enter the number of sheets for any of the

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Description	43 /
Claim(s)	6 /
Abstract	1 /
Drawing(s)	-

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10. If you are also filing any of the following,
state how many against each item

Priority Documents

Translations of priority documents

Statement of inventorship and right
to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination
and search (*Patent Form 9/77*)

Request for substantive examination
(*Patent Form 10/77*)

Any other documents
(*please specify*)

11.

I/We request the grant of a patent on the basis of this application

Judith Pritchard

Signature JUDITH PRITCHARD 21 OCTOBER 2002
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of
person to contact in the United Kingdom

SUE MORTON
01438 76 8612

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a) Notes

If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) *Write your answers in capital letters using black ink or you may type them.*

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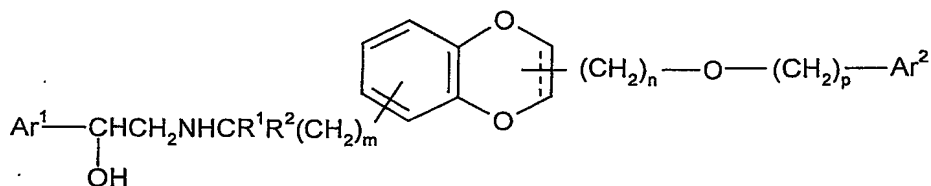
Medicinal Compounds

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2 -adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

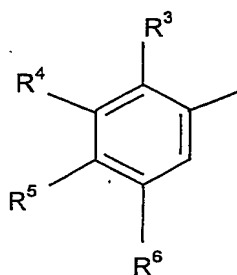
Although salmeterol and the other commercially available β_2 -adrenoreceptor agonists are effective bronchodilators, the maximum duration of action is 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2 -adrenoreceptors and having an advantageous profile of action.

According to the present invention, there is provided a compound of formula (I)

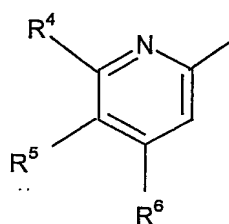


or a salt, solvate, or physiologically functional derivative thereof, wherein:

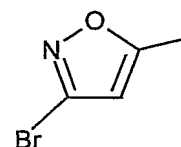
Ar^1 is a group selected from



(a)

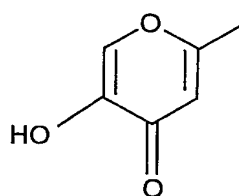


(b)



(c)

and



(d)

wherein R^4 represents halogen, $-(CH_2)_qOR^7$, $-NR^7C(O)R^8$, $-NR^7SO_2R^8$,
 5 $-SO_2NR^7R^8$, $-NR^7R^8$, $-OC(O)R^9$ or $OC(O)NR^7R^8$,
 and R^3 represents hydrogen or C_{1-4} alkyl;

or R^4 represents $-NHR^{10}$ and R^3 and $-NHR^{10}$ together form a 5- or 6- membered
 10 heterocyclic ring;

R^5 represents hydrogen, halogen, $-OR^7$ or $-NR^7R^8$;

R^6 represents hydrogen, halogen, halo C_{1-4} alkyl, $-OR^7$, $-NR^7R^8$, $-OC(O)R^9$ or
 15 $OC(O)NR^7R^8$;

R^7 and R^8 each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^7R^8$, $-SO_2NR^7R^8$, and $-OC(O)NR^7R^8$, R^7 and R^8 independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

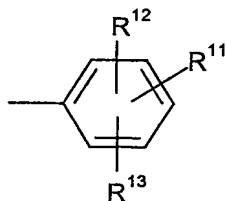
5

R^9 represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

10

q is zero or an integer from 1 to 4;

Ar^2 is a group:



15

wherein

R^{11} is selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, cyano, nitro, halo, C_{1-6} haloalkyl, XCO_2R^{16} , $-XC(O)NR^{15}R^{16}$, $-XNR^{14}C(O)R^{15}$, $-XNR^{14}C(O)NR^{15}R^{16}$, $-XNR^{14}C(O)NC(O)NR^{15}R^{16}$, $-XNR^{14}SO_2R^{15}$, $-XSO_2NR^{17}R^{18}$, XSR^{14} , $XSOR^{14}$, XSO_2R^{14} , $-XNR^{15}R^{16}$, $-XNR^{14}C(O)OR^{15}$, or $XNR^{14}SO_2NR^{15}R^{16}$,
 20 or R^{11} is selected from $-X$ -aryl, $-X$ -hetaryl, or $-X$ -(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6} alkoxy, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, cyano, nitro, $CONR^{15}R^{16}$, $-NR^{14}C(O)R^{15}$, SR^{14} , SOR^{14} , $-SO_2R^{14}$, $-SO_2NR^{17}R^{18}$, $-CO_2R^{16}$, $-NR^{15}R^{16}$, or hetaryl
 25 optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6} alkoxy, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl;

X is $-(CH_2)_r-$ or C_{2-6} alkenylene;

r is an integer from 0 to 6, preferably 0 to 4;

5 R^{14} and R^{15} are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6} alkyl)- and aryl(C_{1-6} alkyl)- and R^{14} and R^{15} are each independently optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, -NHC(O)(C_{1-6} alkyl), -SO₂(C_{1-6} alkyl), -SO₂(aryl), -CO₂H, and -CO₂(C_{1-4} alkyl), -NH₂, -NH(C_{1-6} alkyl), aryl(C_{1-6} alkyl)-, aryl(C_{2-6} alkenyl)-, aryl(C_{2-6} alkynyl)-, hetaryl(C_{1-6} alkyl)-, -NHSO₂aryl, -NH(hetaryl(C_{1-6} alkyl)), -NHSO₂hetaryl, 10 -NHSO₂(C_{1-6} alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

or R^{14} and R^{15} , together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7- membered nitrogen – containing ring;

15 or where R^{11} is -XNR¹⁴C(O)NR¹⁵R¹⁶, R^{14} and R^{15} may, together with the -NC(O)N- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an imidazolidine ring, such as imidazolidine-2,4-dione;

20 or where R^{11} is -XNR¹⁴C(O)OR¹⁵, R^{14} and R^{15} may, together with the -NC(O)O- portion of the group R^{11} to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an oxazolidine ring, such as oxazolidine-2,4-dione;

25 R^{16} is selected from hydrogen, C_{1-6} alkyl and C_{3-7} cycloalkyl;

or where R^{11} is -XC(O)NR¹⁵R¹⁶ or -XNR¹⁴C(O)NR¹⁵R¹⁶, R^{15} and R^{16} may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen 30 containing ring;

R^{17} and R^{18} are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6} alkyl)- and aryl(C_{1-6} alkyl)-, or R^{17} and R^{18} , together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring; and R^{17} and R^{18} are each optionally substituted by one or two groups independently selected from halo, C_{1-6} alkyl, and C_{3-7} cycloalkyl, C_{1-6} haloalkyl;

R^{12} is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halo, aryl, aryl(C_{1-6} alkyl)-, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl;

R^{13} is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halo, aryl, aryl(C_{1-6} alkyl)-, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl;

R^1 and R^2 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^1 and R^2 is not more than 4;

m is an integer of from 1 to 3;

n is an integer of from 1 to 4; and

p is an integer of from 1 to 4;

and --- represents a single or double bond.

In the compounds of formula (I) the group Ar^1 is preferably selected from groups (a) and (b) above. In said groups (a) and (b), when R^4 represents halogen this is preferably chlorine or fluorine. R^7 and R^8 preferably each independently represent hydrogen or methyl. R^9 preferably represents substituted phenyl. The integer q preferably represents zero or 1. Thus for example $-(CH_2)_qOR^7$ preferably represents OH or $-CH_2OH$;

$NR^7C(O)R^8$ preferably represents $-NHC(O)H$;

$-SO_2NR^7R^8$ preferably represents $-SO_2NH_2$ or SO_2NHCH_3 ;

NR^7R^8 preferably represents $-NH_2$;

$-OC(O)R^9$ preferably represents substituted benzoyloxy eg. $OC(O)-C_6H_4-(p-CH_3)$; and

$-OC(O)NR^7R^8$ preferably represents $OC(O)N(CH_3)_2$.

When R^4 represents NHR^{10} and together with R^3 forms a 5- or 6- membered heterocyclic ring $-NHR^{10}-R^3-$ preferably represents a group:

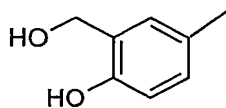
$-NH-CO-R^{19}$ where R^{19} is an alkylene, alkenylene or alkenyloxy group;

$-NH-SO_2R^{20}$ where R^{20} is an alkenyloxy group;

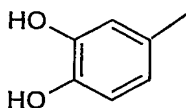
5 $-NH-R^{21}-$ where R^{21} is an alkylene or alkenylene group optionally substituted by $COOR^{22}$ where R^{22} is C_{1-4} alkyl; or

$-NH-CO-CH-$ or $NH-CO-S-$ wherein said alkylene, and alkenylene groups and moieties contain 1 or 2 carbon atoms.

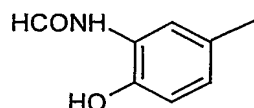
10 Particularly preferred groups (a) and (b) may be selected from the following groups (i) to (xxi):



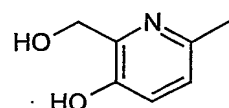
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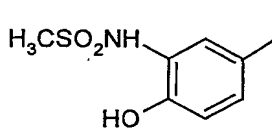
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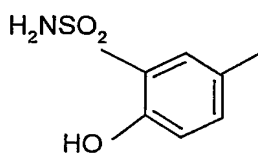
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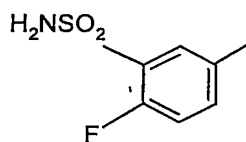
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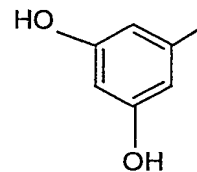
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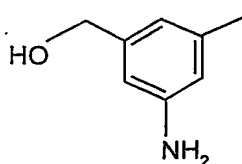
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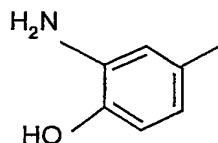
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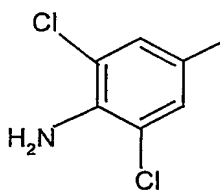
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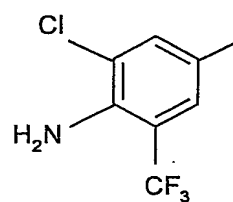
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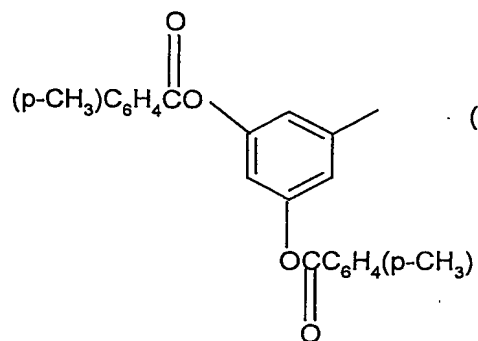
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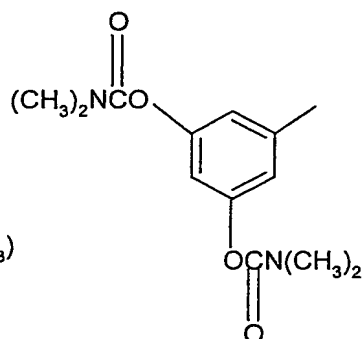
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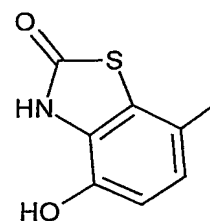
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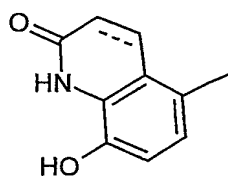
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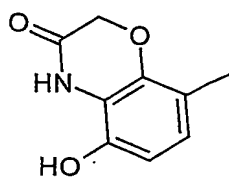
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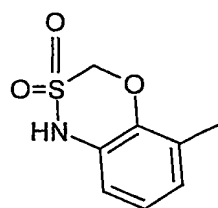
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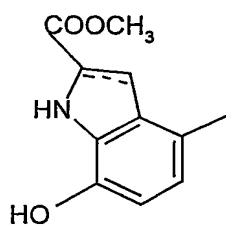
(xvi)



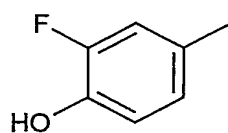
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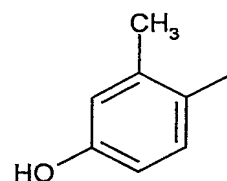
(xviii)



(xix)



(xx)



(xxi)

wherein the dotted line in (xv) represents a single or double bond.

In the compounds of formula (I), in the group Ar^2 the group R^{11} is suitably selected from hydrogen, C_{1-4} alkyl, hydroxy, halo, $-NR^{14}C(O)NR^{15}R^{16}$, and $-NR^{14}SO_2R^{15}$ and $XSO_2NR^{17}R^{18}$ wherein R^{14} to R^{18} are as defined above or more suitably wherein R^{14} is hydrogen and R^{15} is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl and aryl and is optionally substituted as described above.

In the compounds of formula (I) R^{12} and R^{13} preferably each represent hydrogen.

In the compounds of formula (I), R^1 and R^2 are preferably independently selected from hydrogen and methyl, more preferably R^1 and R^2 are both hydrogen.

In the compounds of formula (I), each of m , n and p independently is suitably 1 or 2.

In the compounds of formula (I), the group R^{11} is preferably attached to the meta-position relative to the $-O-(CH_2)_p-$ link.

In the definition of X , the term alkenylene includes both *cis* and *trans* structures.

Examples of suitable alkenylene groups include $-CH=CH-$.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

The compounds of formula (I) include an asymmetric centre, namely the carbon atom of the



group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions. Preferably, the compounds of the invention are in the form of the (R) enantiomers.

Similarly, where R^1 and R^2 are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

Furthermore, when --- represents a single bond, the carbon atom in the benzodioxan ring to which the moiety $\text{---}(\text{CH}_2)_n\text{---}$ is attached will represent a further asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

Thus the compounds of formula (I) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of formula (I) for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballic, cinnamic, substituted cinnamic (for example, phenyl, methyl, methoxy or

halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters of the compounds of formula (I) may have a hydroxyl group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester.

As mentioned above, the compounds of formula (I) are selective β_2 -adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved therapeutic index in animal models relative to existing long-acting β_2 -agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

Therefore, compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

In the alternative, there is also provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated. In particular, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof

in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 100mg per day and preferably 0.01 mg to 1mg per day.

While it is possible for a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and

aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20 μ g-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10 μ m, preferably 2-5 μ m. Particles having a size above 20 μ m are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90 μ m and not less than 15% will have a MMD of less than 15 μ m.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

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Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

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Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

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Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

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It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

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The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M_1 , M_2 , M_1/M_2 or M_3 receptor antagonist), other β_2 -adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, another β_2 -adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional

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derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

- 5 It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate,
10 the therapeutic ingredients may be used in optically pure form.

- Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-
15 inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy- androsta-1,4-diene-17 β -carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone
20 esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester and 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-
25 16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, more preferably 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.
- 30 Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or

antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2 -adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

A method for determining IC_{50} s ratios is set out in US patent 5,998,428 which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/51599 for an another description of said assay.

The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC₅₀ ratio of about 0.1 or greater; said ratio is the ratio of the IC₅₀ value for competing with the binding of 1nM of [³H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC₅₀ value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[³H]-cAMP as the substrate.

Examples of useful PDE4 inhibitors are:

(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone;
cis 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid];
cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol];
(R)-(+)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate; and
(S)-(-)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate.

Most preferred are those PDE4 inhibitors which have an IC₅₀ ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC₅₀ ratio of 0.1 or greater.

Other compounds of interest include:

Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomast) and its salts, esters, pro-drugs or physical forms;

AWD-12-281 from Asta Medica (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vemalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther, 1998, 284(1): 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M₁ and M₂ receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.

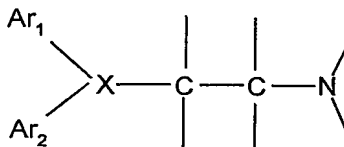
Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

Hyoscyamine (*d, l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt- CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H₁-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H₁-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H₁-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperazine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the

alkylamines) or mimic the tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

5 Ethylenediamines: pyrillamine amleate, tripeleennamine HCl, and tripeleennamine citrate.

Alkylamines: chloropheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

10 Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H₁ receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

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The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

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The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

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The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

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The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.

- 5 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

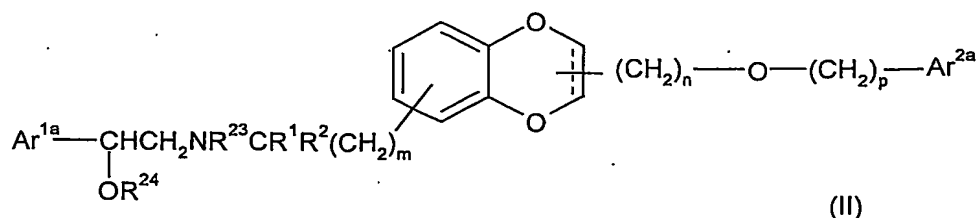
10 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

15 The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

20 According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) or a salt, solvate, or physiologically functional derivative thereof which comprises a process (a), or (b) as defined below, followed by the following steps in any order:

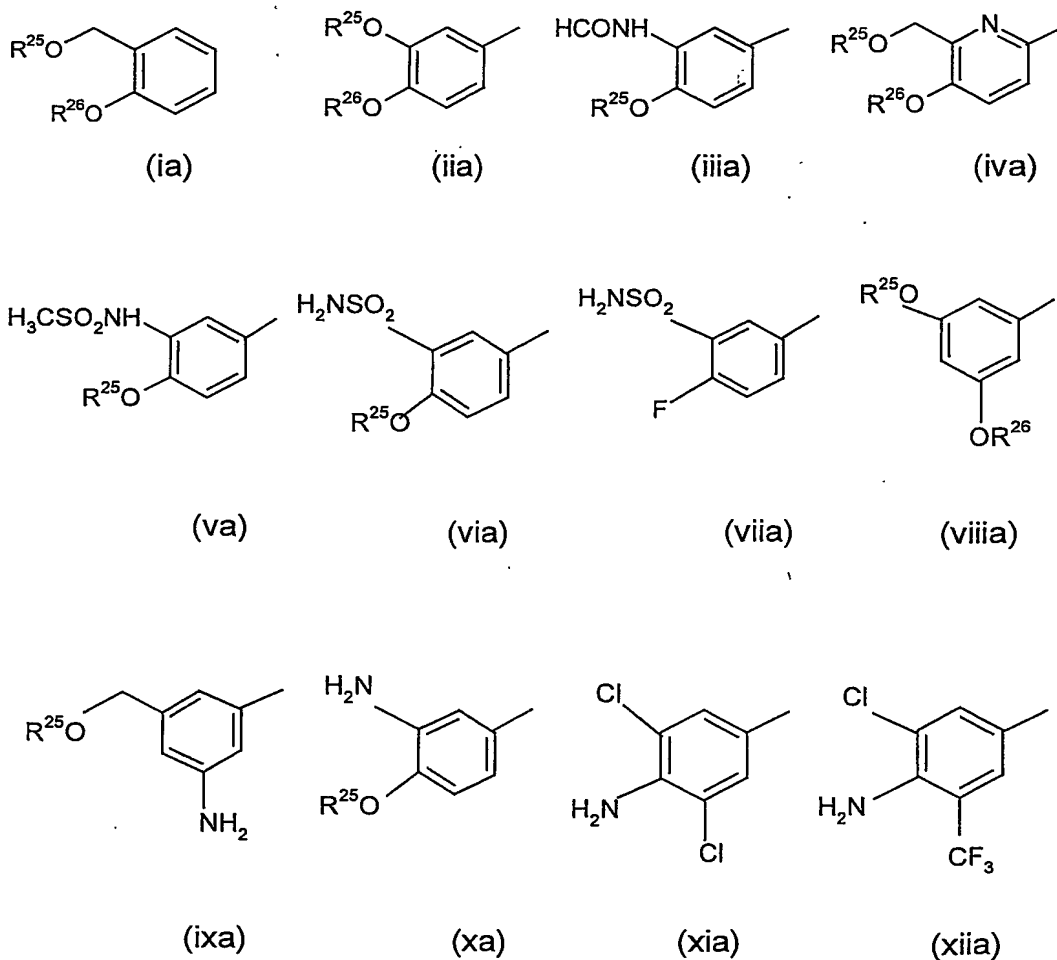
- 25 (i) optional removal of any protecting groups;
 (ii) optional separation of an enantiomer from a mixture of enantiomers;
 (iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

30 In one general process (a), a compound of formula (I), may be obtained by deprotection of a protected intermediate, for example of formula (II):

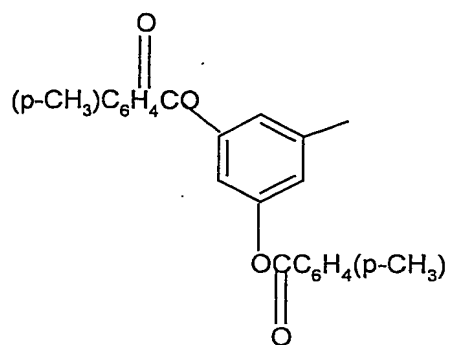


or a salt or solvate thereof, wherein R^1 , R^2 , m , n , p and $---$ are as defined for the compound of formula (I), Ar^{1a} represents an optionally protected form of Ar^1 ; Ar^{2a} represents an optionally protected form of Ar^2 and R^{23} and R^{24} are each independently either hydrogen or a protecting group, provided that the compound of formula (II) contains at least one protecting group.

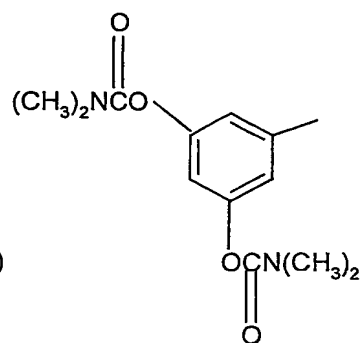
Protected forms Ar^{1a} of the preferred groups Ar^1 may be selected from:



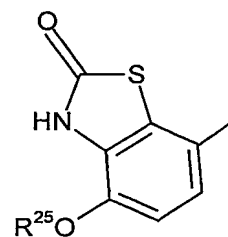
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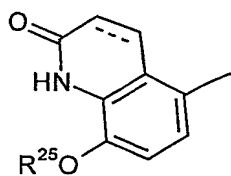
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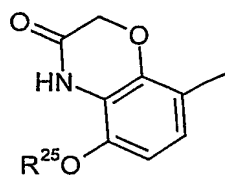
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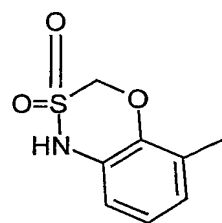
(xva)



(xvia)

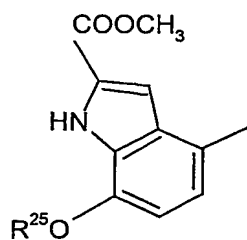


(xviiia)

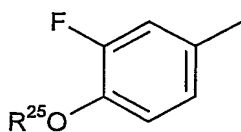


(xviiiia)

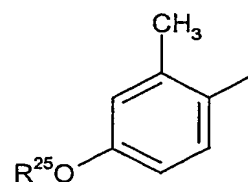
5



(xixa)



(xxa)



(xxia)

wherein R^{25} and R^{26} are each independently either hydrogen or a protecting group provided that at least one of R^{25} and R^{26} is a protecting group.

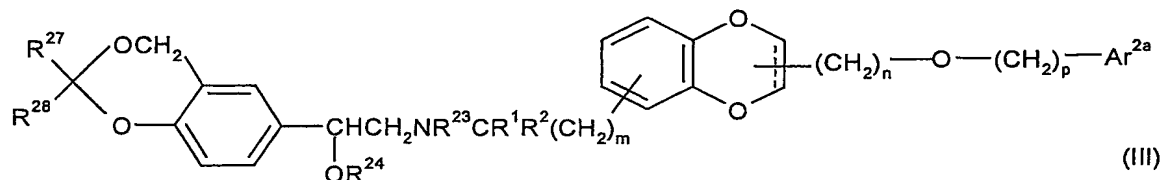
Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by R^{25} and R^{26} are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by R^{23} include benzyl, α -methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the $-\text{CH}(\text{OH})$ group may be orthogonally protected as $-\text{CH}(\text{OR}^{24})$ using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene and Peter G M Wuts (see above).

The deprotection to yield a compound of formula (I), may be effected using conventional techniques. Thus, for example, when R^{25} , R^{26} , and/or R^{23} is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

When R^{25} and/or R^{26} is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by R^{23} may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene and Peter G M Wuts (see above). In a particular embodiment of process (a), R^{25} and R^{26} may together represent a protecting group as in the compound of formula (III):

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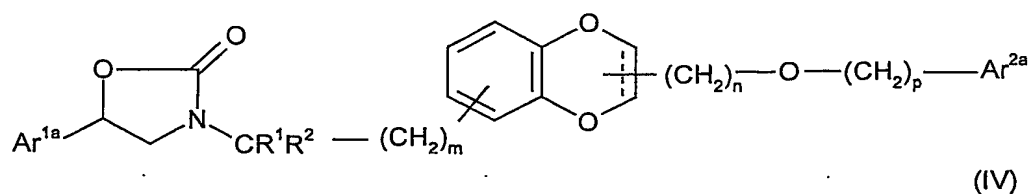


or a salt or solvate thereof, wherein --- , R^1 , R^2 , R^{23} , R^{24} , m , n and p are as defined for the compound of formula (II), R^{27} and R^{28} are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl or R^{27} and R^{28} together form a C_{3-7} cycloalkyl ring. In a preferred aspect, both R^{27} and R^{28} are methyl.

The compound of formula (III) may be converted to a compound of formula (I), by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketalisation in an alcohol, for example ethanol, in the presence of a catalyst such as an acid (for example, toluenesulphonic acid) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

It will be appreciated that the protecting groups R^{25} , R^{26} , R^{23} and R^{24} (including the cyclised protecting group formed by R^{25} and R^{26} as depicted in formula (III) may be removed in a single step or sequentially. The precise order in which protecting groups are removed will in part depend upon the nature of said groups and will be readily apparent to the skilled worker. Preferably, when R^{25} and R^{26} together form a protecting group as in formula (III) this protecting group is removed together with any protecting group on the $\text{CH}(\text{OH})$ moiety, followed by removal of R^{23} .

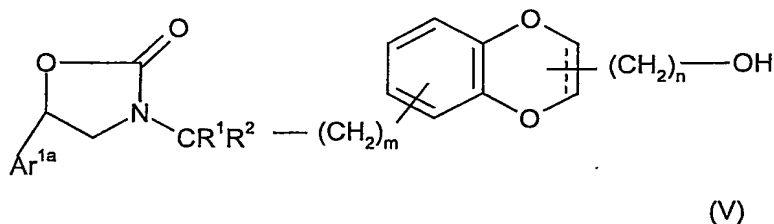
Compounds of formulae (II) and (III) wherein R^{23} is hydrogen may be prepared from the corresponding compound of formula (IV):



or a salt or solvate thereof, wherein --- , Ar^{1a} , Ar^{2a} , R^1 , R^2 , m , n and p are as defined for the compound of formula (II) or (III).

5 The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.

10 Compounds of formula (IV) may be prepared from the corresponding compound of formula (V):



15 or a salt or solvate thereof, wherein Ar^{1a} , R^1 , R^2 , m , n and p are as defined for the compound of formula (II).

by reaction with a compound of formula (VI):

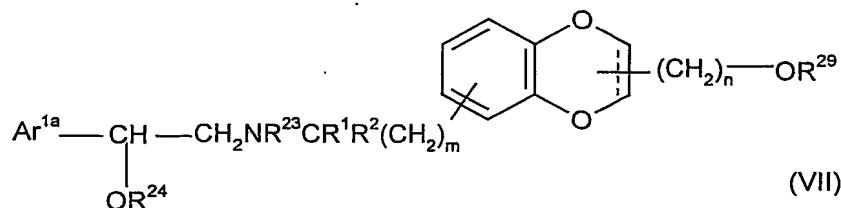


Wherein L is a leaving group.

25 The reaction of a compound of formula (V) with a compound of formula (VI) is conveniently effected in the presence of a base such as sodium hydride in a suitable solvent for example dimethylformamide.

Compounds of formula (VI) are commercially available or may be prepared by methods well known to the person skilled in the art.

Compounds of formula (V) may be prepared from a corresponding compound of formula (VII):



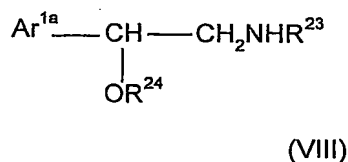
5

Wherein ---, Ar^{1a} , R^1 , R^2 , R^{23} , R^{24} , m and n are as hereinbefore defined for compounds of formula (II), and R^{29} is a protecting group, for example an ester-forming group such as pivaloyl.

10 A compound of formula (VII) may be converted into a compound of formula (V) by reaction with a reagent such as 1,1-carbonyldiimidazole, in a solvent such as tetrahydrofuran. The protecting group R^{29} may be removed by any suitable method known in the art, for example by reaction with a trialkylsilanolate eg. potassium trimethylsilanolate, in a solvent such as tetrahydrofuran.

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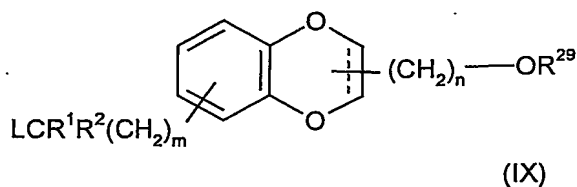
Compounds of formula (VII) may be prepared by reacting a compound of formula (VIII):



Wherein Ar^{1a} , R^{23} and R^{24} are as defined for formula (II).

20

With a compound of formula (IX):



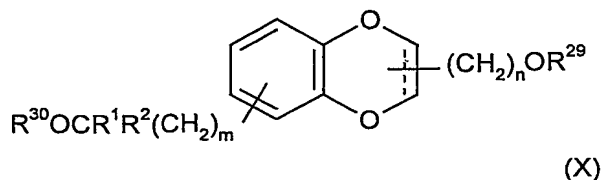
Wherein --- , R^1 , R^2 , m and n are as defined for formula (II) and L is a leaving group for example a halo group, (typically bromo or iodo) or a sulphonate such as an alkyl sulphonate (typically methanesulphonate) an aryl sulphonate (typically toluenesulphonate) or a haloalkylsulphonate (typically trifluoromethanesulphonate).

The reaction of a compound for formula (VIII) with a compound of formula (IX) may conveniently be effected in a solvent such as N,N-dimethylformamide.

Compounds of formula (VIII) are known in the art (for example EPA 0947498) or may be readily prepared by a person skilled in the art using known methods, for example as described in WO 02/066422.

Further details concerning preparation of compounds (VIII) wherein Ar^1 is a group (iv) can be found in DE3524990; concerning the preparation of compounds (VIII) wherein Ar^1 is a group (i), (vii), and (xv) in EP-A-162576; concerning the preparation of compounds (VIII) wherein Ar^1 is a group (iii) in EP-A-22054; concerning the preparation of compounds (VIII) wherein Ar^1 is a group (x) in GB2165542 and concerning the preparation of compounds (VIII) wherein Ar^1 is a group (c) in GB2230523.

Compounds of formula (IX) may be prepared from a corresponding compound of formula (X):

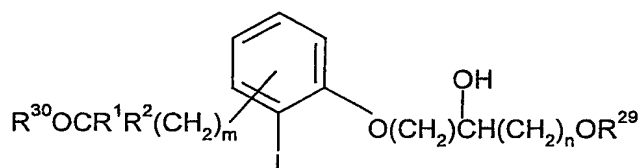


Wherein R^{30} is hydrogen or a protecting group, such as a trialkylsilyl group eg. t-butyl dimethylsilyl, and --- , R^1 , R^2 , m , n and R^{29} are as defined for formula (IX).

Thus for example a compound of formula (X) wherein R^{30} represents hydrogen may be reacted with a sulfonyl halide, eg. methanesulfonyl chloride or p-toluenesulfonyl chloride to give a compound of formula (IX) wherein L is a sulphonate. Said sulfonate may if

desired be converted into a corresponding halide by reaction with a tetraalkylammonium halide, such as tetrabutylammonium iodide, in a suitable solvent, for example acetonitrile. Where R^{30} represents a protecting group this may be removed prior to formation of the group L, by conventional methods. Thus for example when R^{30} represents a trialkylsilyl group this may be removed eg. by reaction with tetrabutylammonium fluoride.

Compounds of formula (X) may be prepared from a compound of formula (XI):



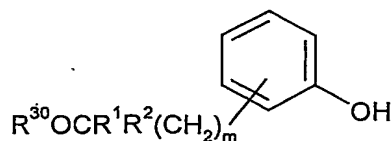
(XI)

Wherein R^1 , R^2 , R^{29} , R^{30} , m and n are as defined for formula (X).

Cyclisation of a compound (XI) may be effected by reaction with a base such as caesium carbonate or potassium carbonate in the presence of cuprous iodide and 1,10-phenanthroline in a solvent such as toluene. If necessary or desired, the product of the cyclisation reaction may be further reacted to introduce the group R^{30} .

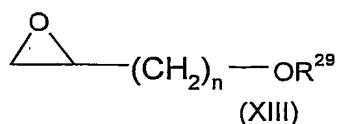
If desired the protecting group R^{29} may be replaced with a different protecting group, using standard deprotection and protection techniques, eg. to facilitate further reaction of a compound (X). Thus for example, in compounds of formula (XI) R^{29} is conveniently benzyl, but in subsequent stages an acyl group such as pivaloyl is preferred.

Compounds of formula (XI) may be prepared by reacting a compound of formula (XII):



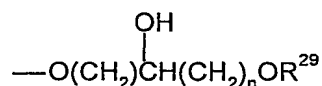
(XII)

Wherein R^1 , R^2 , R^{30} and m are as defined for formula (XI) with a solution of iodine, in the presence of a base such as sodium hydroxide and in a solvent such as ethanol, to form the iodo-substituted compound. This may then be reacted with a compound of formula (XIII):



under basic conditions eg. using caesium carbonate in a solvent such as N,N-dimethylformamide.

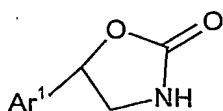
It will be appreciated that the configuration of the moiety :



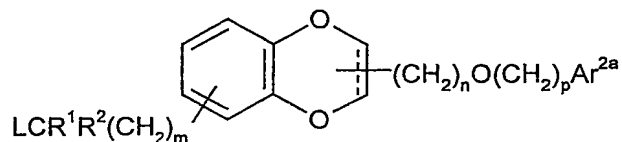
in formula (XI) and ultimately of the compound of formula (I) in respect of the asymmetric carbon atom in the benzodioxan ring will depend upon the configuration of the compound of formula (XIII) employed. In one embodiment, the compound of formula (XIII) may be for example (S)-(+)-benzyl glycidyl ether.

Compounds of formula (XII) and (XIII) are commercially available or may be prepared by standard methods.

Compounds of formula (V) may also be prepared by reaction of a compound of formula



or a salt or solvate thereof, wherein Ar^1 is as defined for the compound of formula (II) with a compound of formula:



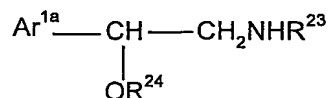
(XV)

wherein --- , R^1 , R^2 , R^{2a} , m , n and p are as defined for the compound of formula (II) and L is a leaving group as defined for formula (IX)

The coupling of a compound of formula (XIV) with a compound of formula (XV) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as cesium carbonate, in an aprotic solvent, for example N,N-dimethylformamide or tetrahydrofuran.

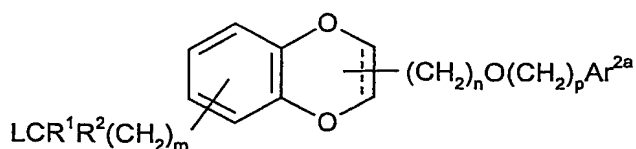
Compounds of formula (XIV) may be prepared as described in WO 02/066422.

In a further process (b) a compound of formula (I), (II) or (III) may be prepared by alkylation of an amine of formula



(VIII)

Wherein Ar^{1a} , R^{23} and R^{24} are as defined for formula (II) with a compound of formula (XV)



(XV)

as defined above

5 followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II) and (III).

10 The reaction of compounds (VIII) and (XV) is optionally effected in the presence of an organic base such as trialkylamine and in a suitable solvent, for example N,N-dimethyl formamide or acetonitrile.

15 It will be appreciated that in either of the routes (a) or (b) described above, the precise order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly.

20 The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral intermediates by the methods described above.

25 Optional conversions of a compound of formula (I) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

30 According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I) for example: compounds of formula (II), (III) and (IV) as defined above, or an optical isomer, a salt, or a protected derivative thereof

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

5 Throughout the examples, the following abbreviations are used:

LCMS: Liquid Chromatography Mass Spectrometry

MS : mass spectrum

TSP+ve : thermospray mass spectrum positive mode

HPLC: high pressure liquid chromatography

10 RT : retention time

THF : tetrahydrofuran

DCM : dichloromethane

DMF : N,N-dimethylformamide

EtOAc : ethyl acetate

15 Et₂O : diethyl ether

EtOH : ethanol

MeOH : methanol

bp : boiling point

ca : circa

20 h : hour(s)

min : minute(s)

All temperatures are given in degrees centigrade.

Silica gel refers to Merck silica gel 60 Art number 7734.

Flash silica gel refers to Merck silica gel 60 Art number 9385.

25 Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.

Bond Elut are prepacked cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.

30 LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO₂H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5 min 0%B at a flow rate of

3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

HPLC was conducted on a LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% formic acid and 0.01 M ammonium acetate in water (solvent A), and 0.05% formic acid 5% water in acetonitrile (solvent B) using the following elution gradient 0-1 min 0%B, 1-10 min 100%B, 10-13 min 100%B, 13-15 min 0%B at a flow rate of 1 ml/min

Example 1

4-((1*R*)-2-[[2-((3*R*)-3-[(2,6-Dichlorobenzyl)oxy]methyl)-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol with (2*E*)-but-2-enedioic acid (1:2)

i) 4-(2-Hydroxyethyl)-2-iodophenol

A solution of iodine (100g) in ethanol (900ml) was added slowly over 2h to a stirred solution of 4-hydroxy phenethylalcohol (54.8g) in 2M sodium hydroxide solution (900ml) at room temperature. The solution was concentrated (ca 50% vol), acidified with 50% hydrochloric acid and extracted with ethyl acetate. The extracts were washed with aqueous sodium sulphite (300ml), water and dried (Na₂SO₄). The solvent was evaporated to dryness to give a brown solid, which was crystallised from light petroleum (40-60)-ethyl acetate (2:1, 700ml) to give light brown plates (34.7g). The mother liquors were evaporated onto silica (merck 9385) and purified by flash chromatography (500g) eluting with dichloromethane-2-propanol (95:5). The appropriate fractions were combined with the first batch and re-crystallised from light petroleum (40-60)-ethyl acetate (2:1, 500ml) to give *the title compound* as a pale brown crystalline solid (27.6g). LCMS RT = 2.75 min. Concentration of the mother liquors gave a second crop (24.3g).

ii) (2*R*)-1-(Benzyloxy)-3-[4-(2-hydroxyethyl)-2-iodophenoxy]propan-2-ol

A stirred mixture of 4-(2-hydroxyethyl)-2-iodophenol (36g), (S)-(+)-benzyl glycidyl ether (25g) and caesium carbonate (53g) in dimethylformamide (600ml) was heated at 90 °C for 18h. The mixture was cooled, poured into 2M hydrochloric acid and extracted into ethyl acetate. The combined extracts were washed with 2M sodium hydroxide, water,

dried (Na_2SO_4) and evaporated. The residual solid was triturated under ether (200ml) to give *the title compound* as a pale brown solid (44g). LCMS RT = 3.35 min.

iii) 2-[(3R)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol

5 A stirred mixture of (2R)-1-(benzyloxy)-3-[4-(2-hydroxyethyl)-2-iodophenoxy]propan-2-ol (44g), caesium carbonate (66g), cuprous iodide (1.9g) and 1,10 phenanthroline (1.9g) in toluene (400ml) was heated at 110 °C for 18h. The mixture was cooled, filtered through celite and the filtrate evaporated with silica gel (200g). The residue was purified by flash chromatography (600g) eluting with ether to give *the title compound* as an oil (25g). LCMS RT = 3.37 min.

iv) 2-[(3R)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl]ethyl methanesulfonate

15 Methanesulphonyl chloride (8.8ml) was added to stirred, cooled (ice-bath) solution of 2-[(3R)-3-[(benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol (19g) in pyridine (120ml). The solution was then stirred for 1.5 h at room temperature. The solution was then poured into 5M hydrochloric acid (600ml) and extracted into dichloromethane. The extracts were washed with saturated sodium bicarbonate solution, water and dried (Na_2SO_4). The solvent was evaporated and the residual oil was purified by flash chromatography (merck 9385, 600g) eluting with ether-cyclohexane (4:1). The appropriate fractions were evaporated to give *the title compound* as a clear oil (19g). LCMS RT = 3.44 min.

v) 2-[(3R)-3-(Hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethyl methanesulfonate

25 A solution of 2-[(3R)-3-[(benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl]ethyl methanesulfonate (19g) in ethanol (400ml) and ethyl acetate (400ml) was hydrogenated over 10% palladium on carbon (3g) and 20% palladium hydroxide on carbon (60% paste in water, 7g) for 24 h at room temperature. The catalysts were filtered through celite and the filtrate was evaporated to dryness to give *the title compound* as an oil (15g). LCMS RT = 2.42 min.

vi) [(2S)-7-{2-[(Methylsulfonyl)oxy]ethyl}-2,3-dihydro-1,4-benzodioxin-2-yl)methyl pivalate

Pivaloyl chloride (15.6ml) was added to a stirred, and cooled (ice-bath) solution of 2-[(3R)-3-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethyl methanesulfonate (15g) in pyridine (120ml). The solution was stirred at room temperature for 1h, then poured into 5M hydrochloric acid (500ml) and extracted into dichloromethane. The extracts were washed with a saturated sodium bicarbonate solution, water, dried (Na₂SO₄) and evaporated to give *the title compound* as an oil (19g). LCMS RT = 3.3 min.

vii) [(2S)-7-(2-Iodoethyl)-2,3-dihydro-1,4-benzodioxin-2-yl)methyl pivalate

A solution of [(2S)-7-{2-[(methylsulfonyl)oxy]ethyl}-2,3-dihydro-1,4-benzodioxin-2-yl)methyl pivalate (13g) and tetrabutylammonium iodide (52g) in acetonitrile (200ml) was heated at 70 °C for 4h. The solvent was concentrated to near dryness, diluted with water (800ml) and extracted with ether (500ml). The organic extract was washed with water, dried (Na₂SO₄) and evaporated to give *the title compound* as an oil (13.5g). LCMS RT = 3.88 min.

viii) [(2S)-7-(2-{[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}ethyl)-2,3-dihydro-1,4-benzodioxin-2-yl)methyl pivalate

A mixture of [(2S)-7-(2-iodoethyl)-2,3-dihydro-1,4-benzodioxin-2-yl)methyl pivalate (4.4g) and (1R)-2-amino-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (WO 02/070490) (4.8g) in dimethylformamide (15ml) was stirred for 20 h at room temperature. The mixture was poured into water and extracted into ether. The combined extracts were washed with water, dried (Na₂SO₄) and evaporated to dryness. The residual oil was purified on a biotage cartridge (90g) eluting with dichloromethane-ethanol-0.88 ammonia (200:8:1) to give *the title compound* as an oil (1.7g). LCMS RT = 2.66 min.

ix) [(2S)-7-{2-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}-2,3-dihydro-1,4-benzodioxin-2-yl)methyl pivalate

1,1 Carbonyl diimidazole (1.6g) was added to a stirred solution of [(2S)-7-(2-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}ethyl)-2,3-dihydro-1,4-benzodioxin-2-yl)methyl pivalate (3.3g) in dry tetrahydrofuran (50ml). After 18h the

solution was evaporated to dryness, diluted with water (100ml) and extracted into ether. The extracts were dried (Na₂SO₄), evaporated and the residual oil was purified on a biotage cartridge (90g) using ether as eluent. The fractions were evaporated to give *the title compound* as a foam (2.9g). LCMS RT = 3.64 min.

5

x) (1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-({2-[(3*R*)-3-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethyl}amino)ethanol

A solution of ((2*S*)-7-{2-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]ethyl}-2,3-dihydro-1,4-benzodioxin-2-yl)methyl pivalate (2.9g) and potassium trimethylsilanolate (2.8g) in tetrahydrofuran (50ml) was stirred for 2 h at room temperature. The solution was poured into water and extracted into dichloromethane. The extracts were dried (Na₂SO₄) and evaporated to give *the title compound* as a foam (1.7g). LCMS RT = 2.91 min.

15

xi) (5*R*)-3-[2-((3*R*)-3-[(2,6-Dichlorobenzyl)oxy]methyl)-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Sodium hydride (60% dispersion in oil, 0.02g) was added to a solution of (1*R*)-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-({2-[(3*R*)-3-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethyl}amino)ethanol (0.121g) in dimethylformamide (4ml) at room temperature. After 15 min 2,6 dichlorobenzyl bromide (0.1g) was added and the mixture was stirred for 1h. The mixture was then poured into aqueous ammonium chloride solution and extracted into ethyl acetate. The extracts were washed with water, dried (Na₂SO₄) and evaporated. The residual oil was purified on a biotage cartridge (8g) eluting with ether. The appropriate fractions were evaporated to give *the title compound* as an oil (0.108g). LCMS RT = 3.87 min.

25

xii) (1*R*)-2-{2-((3*R*)-3-[(2,6-Dichlorobenzyl)oxy]methyl)-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl}amino}-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

A stirred solution of (5*R*)-3-[2-((3*R*)-3-[(2,6-dichlorobenzyl)oxy]methyl)-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (0.108g) and potassium trimethylsilanolate (0.248g) in tetrahydrofuran (5ml) was heated at 80 °C for 1 h. The mixture was poured into phosphate buffer solution (pH 5) and extracted into ethyl acetate. The extracts were washed with water, dried (Na₂SO₄) and

30

evaporated. The residual oil was purified on a biotage cartridge (4g) eluting with dichloromethane-ethanol-0.88 ammonia. The appropriate fractions were evaporated to give *the title compound* as an oil (0.058g) LCMS RT = 3.00 min.

5 xiii) 4-((1*R*)-2-([2-((3*R*)-3-[(2,6-Dichlorobenzyl)oxy]methyl)-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol with (2*E*)-but-2-enedioic acid (1:2)

A stirred solution of (1*R*)-2-([2-((3*R*)-3-[(2,6-dichlorobenzyl)oxy]methyl)-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino)-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (0.05g)
 10 in glacial acetic acid (5ml) and water (0.3ml) was heated at 80 °C for 1h. The solvent was evaporated and the residual oil purified on a biotage cartridge (4g) eluting with dichloromethane-ethanol-0.88 ammonia (25:8:1). The appropriate fractions were evaporated and the residual oil was dissolved in methanol (5ml), treated with 0.5 equivalent of fumaric acid. The solvent was removed to give *the title compound* as a
 15 foam (0.25g). LCMS RT = 2.66 min; ES+ve 537 (MH⁺).

Example 2

4-((1*R*)-2-([2-((3*R*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

20

i) (1*R*)-2-([2-((3*R*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino)-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

Prepared using methods similar to those described in Example 1 viii) LCMS RT = 2.72 min.

25

ii) 4-((1*R*)-2-([2-((3*R*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

Prepared using methods similar to those described in Example 1 xiii) LCMS RT = 2.60 min; ES+ve 466 (MH)⁺

30

Example 3

5 4-[(1*R*)-2-[(2-[(3*S*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl)amino]-1-hydroxyethyl]-2-(hydroxymethyl)phenol acetate

i) 4-(2-[(*tert*-Butyl(dimethyl)silyl]oxy)ethyl)-2-iodophenol

tert-Butyl dimethylsilyl chloride (1.21g) was added to a stirred solution of 4-(2-hydroxyethyl)-2-iodophenol (2.0g) and imidazole (0.54g) in dimethylformamide (15ml). After 1 h the solution was poured into water and extracted into ether. The extracts were
10 dried (Na₂SO₄), evaporated and the residual oil was purified on a biotage cartridge (40g) using hexane-ether (7:3) as the eluent. The fractions were evaporated to give *the title compound* as a solid (2.2g). LCMS RT = 4.07 min.

ii) (2*S*)-1-(Benzyloxy)-3-[4-(2-[(*tert*-butyl(dimethyl)silyl]oxy)ethyl)-2-iodophenoxy]propan-2-ol

15 A stirred mixture of 4-(2-[(*tert*-butyl(dimethyl)silyl]oxy)ethyl)-2-iodophenol (0.5g), (*R*)-(-)-benzyl glycidyl ether (0.26g) and potassium carbonate (0.219g) in dimethylformamide (1ml) was heated at 90 °C for 1 h. The mixture was cooled, diluted with dichloromethane (20ml) and filtered through celite. The filtrate was evaporated and the residual oil was purified on a biotage cartridge (8g) using hexane-ether (4:1) as eluent.
20 The fractions were evaporated to give *the title compound* as a clear oil (0.306g). LCMS RT = 4.31 min.

iii) (2-[(3*S*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl]ethoxy)(*tert*-butyl)dimethylsilane

Prepared using methods similar to those described in Example 1 iii) LCMS RT =
25 4.31min.

iv) 2-[(3*S*)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol

A solution of (2-((3S)-3-[(benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl)ethoxy)(*tert*-butyl)dimethylsilane (0.15g) and tetrabutylammonium fluoride on silica (1.6g) in tetrahydrofuran (10ml) was stirred for 2 h at room temperature. The mixture was filtered through celite and the filtrate evaporated to dryness. The residual oil was purified on a biotage cartridge (4g) eluting with hexane-ether (3:2). The fractions were evaporated to give *the title compound* as a clear oil (0.07g). LCMS RT = 3.11 min.

v) 2-((3S)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl 4-methylbenzenesulfonate

Prepared using methods similar to those described in Example 1 iv) LCMS RT = 3.87min.

vi) (1R)-2-[(2-((3S)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl)amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

Prepared using methods similar to those described in Example 1 viii)

LCMS RT = 2.86 min.

4-((1R)-2-[(2-((3S)-3-[(Benzyloxy)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl)ethyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol acetate

Prepared using methods similar to those described in Example 1 xiii)

LCMS RT = 2.50 min; ES+ve 466 (MH⁺).

BIOLOGICAL ACTIVITY

5 The potencies of the aforementioned compounds were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human beta 2 adrenoreceptor, compounds of examples 1-3 had IC₅₀ values
10 below 1 μ M.

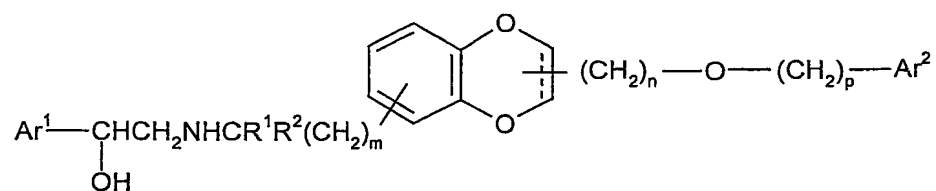
15 Potency at other beta adrenoreceptor subtypes was determined using chinese hamster ovary cells transfected with either the human beta 1 adrenoreceptor or the human beta 3 adrenoreceptor. Agonist activity was assessed by measuring changes in intracellular cyclic AMP.

20 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A compound of formula (I):

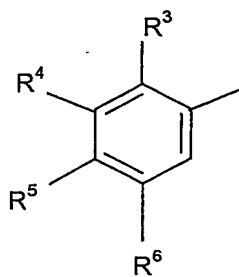
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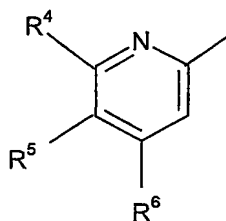
or a salt, solvate, or physiologically functional derivative thereof, wherein:

10

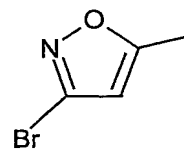
Ar¹ is a group selected from



(a)

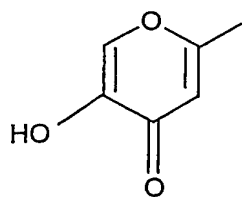


(b)



(c)

and



(d)

wherein R^4 represents halogen, $-(CH_2)_qOR^7$, $-NR^7C(O)R^8$, $-NR^7SO_2R^8$,
 $-SO_2NR^7R^8$, $-NR^7R^8$, $-OC(O)R^9$ or $OC(O)NR^7R^8$,
 and R^3 represents hydrogen or C_{1-4} alkyl;

- 5 or R^4 represents $-NHR^{10}$ and R^3 and $-NHR^{10}$ together form a 5- or 6- membered heterocyclic ring;

R^5 represents hydrogen, halogen, $-OR^7$ or $-NR^7R^8$;

- 10 R^6 represents hydrogen, halogen, halo C_{1-4} alkyl, $-OR^7$, $-NR^7R^8$, $-OC(O)R^9$ or $OC(O)NR^7R^8$;

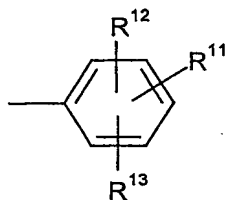
- R^7 and R^8 each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^7R^8$, $-SO_2NR^7R^8$ and $-OC(O)NR^7R^8$, R^7 and R^8 independently represent hydrogen or
 15 C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

- R^9 represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl,
 20 hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

q is zero or an integer from 1 to 4;

Ar^2 is a group:

25



wherein

R^{11} is selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, cyano, nitro, halo, C_{1-6} haloalkyl, XCO_2R^{16} , $-XC(O)NR^{15}R^{16}$, $-XNR^{14}C(O)R^{15}$, $-XNR^{14}C(O)NR^{15}R^{16}$, $-XNR^{14}C(O)NC(O)NR^{15}R^{16}$, $-XNR^{14}SO_2R^{15}$, $-XSO_2NR^{17}R^{18}$, XSR^{14} , $XSOR^{14}$, XSO_2R^{14} , $-XNR^{15}R^{16}$, $-XNR^{14}C(O)OR^{15}$, or $XNR^{14}SO_2NR^{15}R^{16}$,

or R^{11} is selected from $-X$ -aryl, $-X$ -hetaryl, or $-X$ -(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6} alkoxy, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, cyano, nitro, $CONR^{15}R^{16}$, $-NR^{14}C(O)R^{15}$, SR^{14} , SOR^{14} , $-SO_2R^{14}$, $-SO_2NR^{17}R^{18}$, $-CO_2R^{16}$, $-NR^{15}R^{16}$, or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6} alkoxy, halo, C_{1-6} alkyl, or C_{1-6} haloalkyl;

X is $-(CH_2)_r-$ or C_{2-6} alkenylene;

r is an integer from 0 to 6, preferably 0 to 4;

R^{14} and R^{15} are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6} alkyl)- and aryl(C_{1-6} alkyl)- and R^{14} and R^{15} are each independently optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, $-NHC(O)(C_{1-6}alkyl)$, $-SO_2(C_{1-6}alkyl)$, $-SO_2(aryl)$, $-CO_2H$, and $-CO_2(C_{1-4}alkyl)$, $-NH_2$, $-NH(C_{1-6}alkyl)$, aryl($C_{1-6}alkyl$)-, aryl($C_{2-6}alkenyl$)-, aryl($C_{2-6}alkynyl$)-, hetaryl($C_{1-6}alkyl$)-, $-NHSO_2aryl$, $-NH(hetarylC_{1-6}alkyl)$, $-NHSO_2hetaryl$, $-NHSO_2(C_{1-6}alkyl)$, $-NHC(O)aryl$, or $-NHC(O)hetaryl$:

or R^{14} and R^{15} , together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7- membered nitrogen – containing ring;

or where R^{11} is $-XNR^{14}C(O)NR^{15}R^{16}$, R^{14} and R^{15} may, together with the $-NC(O)N$ -portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an imidazolidine ring, such as imidazolidine-2,4-dione;

or where R^{11} is $-XNR^{14}C(O)OR^{15}$, R^{14} and R^{15} may, together with the $-NC(O)O-$ portion of the group R^{11} to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an oxazolidine ring, such as oxazolidine-2,4-dione;

5

R^{16} is selected from hydrogen, C_{1-6} alkyl and C_{3-7} cycloalkyl;

or where R^{11} is $-XC(O)NR^{15}R^{16}$ or $-XNR^{14}C(O)NR^{15}R^{16}$, R^{15} and R^{16} may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

10

R^{17} and R^{18} are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6} alkyl)- and aryl(C_{1-6} alkyl)-, or R^{17} and R^{18} , together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring; and R^{17} and R^{18} are each optionally substituted by one or two groups independently selected from halo, C_{1-6} alkyl, and C_{3-7} cycloalkyl, C_{1-6} haloalkyl;

15

R^{12} is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halo, aryl, aryl(C_{1-6} alkyl)-, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl;

20

R^{13} is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halo, aryl, aryl(C_{1-6} alkyl)-, C_{1-6} haloalkoxy, and C_{1-6} haloalkyl;

R^1 and R^2 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^1 and R^2 is not more than 4;

25

m is an integer of from 1 to 3;

n is an integer of from 1 to 4; and

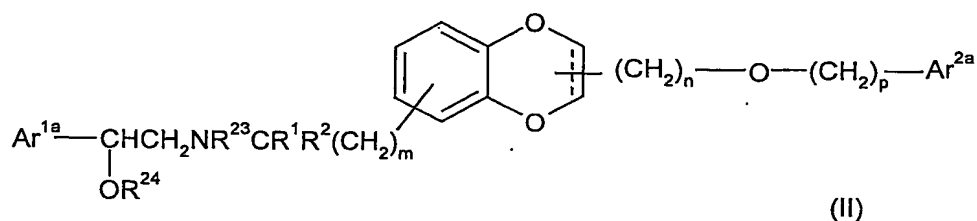
p is an integer of from 1 to 4;

30

and --- represents a single or double bond.

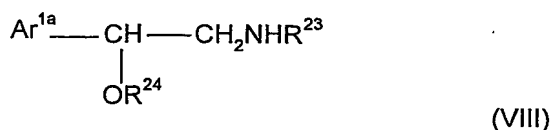
2. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.
3. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.
4. A pharmaceutical formulation comprising a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
5. The use of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated.
6. A process for the preparation of a compound of formula (I), according to claim 1, or a salt, solvate, or physiologically functional derivative thereof, which comprises:

(a) deprotection of a protected intermediate, for example of formula (II).

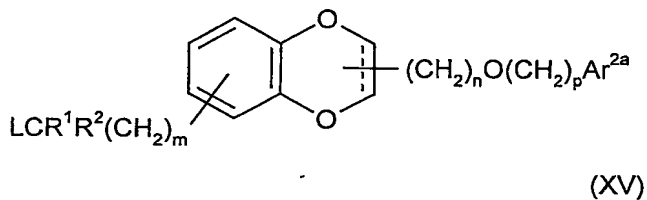


or a salt or solvate thereof, wherein R^1 , R^2 , m , n , p and --- are as defined for the compound of formula (I), Ar^{1a} represents an optionally protected form of Ar^1 ; Ar^{2a} represents an optionally protected form of Ar^2 and R^{23} and R^{24} are each independently either hydrogen or a protecting group, provided that the compound of formula (II) contains at least one protecting group;

(b) alkylation of an amine of formula



Wherein Ar^{1a} , R^{23} and R^{24} are as defined for formula (II) with a compound of formula (XV):



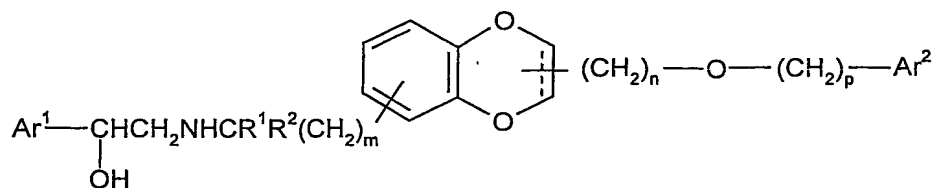
Wherein --- , Ar^2 , R^1 , R^2 , R^{29} , m , n and p are as defined for the compound of formula (II) and L is a leaving group as defined for formula (IX);

followed by the following steps in any order:

- (i) optional removal of any protecting groups;
- (ii) optional separation of an enantiomer from a mixture of enantiomers;
- (iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

ABSTRACT

The present invention relates to novel compounds of formula (I),



and salts, solvates and physiologically acceptable derivatives thereof,
to a process for their manufacture, to pharmaceutical compositions containing them,
10 and to their use in therapy, in particular their use in the prophylaxis and treatment of
respiratory diseases.